enable one skilled in the art to make and/or use the claimed invention. The Examiner asserted that the present specification teaches only nuclease resistance in cells *in vitro*, and no further guidance is provided for the successful delivery of such ribozymes to cells. Applicant respectfully traverses this rejection.

Initially, Applicant requests that the Examiner again note the Declaration of Dan T. Stinchcomb, Ph.D. submitted in Applicant's preceding response. As indicated in that response, that Declaration demonstrates that the claimed invention can be practiced for *in vivo* delivery of ribozymes without undue experimentation. In particular, the Stinchcomb Declaration described two examples of *in vivo* delivery and subsequent target RNA cleavage use two different delivery techniques.

In addition to the foregoing, Applicant now provides three more exemplary references that describe the delivery of modified ribozymes in *in vivo* animal model systems with consequent biological effect. These references are recent publications that demonstrate that one skilled in the art would be able to successfully use the present modified ribozymes *in vivo*. Copies of the references are provided for the Examiner's convenience.

First, Sioud & Sørensen (1998) *Nature Biotechnology* 16:557-562 describes delivery and tumor inhibition of glioma tumors in rats using 2'-amino pyrimidine modified ribozymes complexed with cationic lipids (see, e.g., Abstract).

Likewise, Parry et al., (1999) *Nucleic Acids Research* 27:2569-77, described the use of anti-*flt-1* and anti-*KDR* ribozymes in a rat corneal pocket assay of VEGF-induced angiogenesis. Modified ribozymes having 2'-O-methyl modifications along with either 2'-NH_2 uridine or 2'-C-allyl uridine modifications were used (p.2570, first partial paragraph and Table 1 on p.2571).

A third reference is Frimerman et al. (1999). This reference describes the use of modified ribozymes (RNA-DNA chimera) targeted to both human and pig proliferating cell nuclear antigen (PCNA). The ribozymes were complexed with the cationic lipid LipofectAMINE®. The ribozymes were administered in a porcine model of injury-induced intimal hyperplasia by infusion into the artery wall at the site of stent placement.

If the Examiner regards additional examples of model system delivery of ribozymes as useful, such additional descriptions can be provided.

Still further, human clinical trials have been performed using modified ribozymes. Brief reports of such a trial is available, for example, at www.rpi.com. under Investor Relations/Press Releases, 11/16/99 New Cancer Drug in Multi-dose Safety and Efficacy Studies, along with a report of an IND application to allow clinical trial of an anti-Hepatitis C ribozyme. Such trials demonstrate the *in vivo* delivery of modified ribozymes in humans.

In summary, the exemplary references just described and the reported clinical trials, in conjunction with the Stinchcomb Declaration establish that one skilled in the art can practice the claimed invention without undue experimentation, and that the present claimed invention is properly enabled. Therefore, Applicant respectfully requests that the Examiner reconsider and withdraw the present rejection.

Applicant respectfully submits that the claims are in condition for allowance, and requests a notice to that effect.

Applicant hereby requests a two-month extension of time to allow timely response up to and including January 16, 2000. Kindly charge the fee for that extension (small entity) to Deposit Account 12-2475. If any additional fee is due in connection with this communication, kindly charge the appropriate amount to Deposit Account No. 12-2475.

Respectfully submitted,

LYON & LYON LLP

Dated: 12 January 2000

By: _____
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